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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/662,678	09/15/2003	John P. Troup	8493-US	1877

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12 Vreeland Road, 2nd Floor, Box 697
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EXAMINER	
HA, JULIE	

ART UNIT	PAPER NUMBER
1654	

NOTIFICATION DATE	DELIVERY MODE
02/01/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/662,678	TROUP ET AL.	
	Examiner	Art Unit	
	JULIE HA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-14 and 16-28* is/are pending in the application.

4a) Of the above claim(s) *6,12 and 18-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-11,13-14,16-17, 23-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment after non-final office action filed on October 01, 2009 is acknowledged. Claims 1-4, 6-14, 16-28 are pending in this application. Claims 6, 12 and 18-22 remain withdrawn from further consideration, as being drawn to nonelected inventions and species. Claims 1-4, 7-11, 13-14, 16-17 and 23-28 are examined on the merits in this office action. After further review, a non final office action follows below.

Withdrawn Objection

1. Objection to claim 27 for having minor informality is hereby withdrawn in view of Applicant's amendment to the claim.

Maintained Rejection

35 U.S.C. 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. Claims 1-4, 7-11, 13-14, 16 and 23-26 remain rejected under 35 U.S.C. 102(b) as being anticipated by Abbruzzese et al (US Patent No. 6,077,828, filed with IDS).

4. Abbruzzese et al teach nutritional compositions for the prevention of cachexia and anorexia. The reference teaches a composition comprising effective amounts of ω-3 fatty acids, such as alpha-linolenic acid, stearidonic acid, eicosapentanenoic acid, docosapentaenoic acid, docosahexanoic acid or mixtures thereof; of branched-chain amino acids valine, leucine, isoleucine or mixtures thereof; with or without reduced levels of tryptophan and 5-hydroxytryptophan; and of antioxidant system selected from the group consisting of beta-carotene, vitamin C, vitamin E, selenium or mixtures thereof (see abstract). The reference teaches a liquid nutritional composition comprising (a) at least 1000 mg per liter of ω-3 fatty acids, wherein the weight ratio of ω-6 fatty acids to ω-3 fatty acids is from about 0.1 to about 1.0; (b) at least 50 grams per liter of a source of amino nitrogen, wherein 15 to 50% by weight of the amino-nitrogen is branched-chain amino acids, and wherein tryptophan is present in an amount less than about 5.0% by weight of the total amino -nitrogen, and (c) at least 1 gram per liter of an antioxidant system comprising beta-carotene, vitamin C, vitamin E and selenium (see claim 1). The reference teaches that the total amount of branched-chain amino acids ("BCAA") useful in the present invention is about 15-50 g/100 g protein (i.e. percent), preferably about 15-25 g/100 g. Thus, an 8 oz container of the nutritional composition would contain up to about 8 g BCAAs per 16 grams of total protein. The daily delivery of BCAAs is about 5-26 g (see column 9, lines 26-31). The reference teaches the branched-chain amino acids valine, leucine, isoleucine or mixtures thereof (see

abstract). Therefore, since there is 9.08 g and total of 19.75 g of BCAA, 9.08/19.75 is about 46% of the leucine in the BCAA. Since the reference teaches that the total amount of BCAA useful in the present invention is about 15-50 g/100 g protein, and there is 46% of leucine in the BCAA composition, this implies that there is at least about 23% of leucine. Additionally, the reference teaches that the nutritional compositions comprises branched-chain amino acids, valine, leucine, isoleucine or mixtures of thereof. It is noted that claims 1-3 and 23-25 have been rejected over the prior art, even though the reference does not disclose exact % range as claimed. However, both the claims and the reference utilize the term "about" when discussing the amount of leucine (branched-chain amino acid). It is the term "about" allows for some tolerance in the ranges disclosed. In *In re Ayers*, the Federal Circuit held that "at least about 10%" was anticipated by a reference that disclosed "about 8%" because the term "about" allowed for some tolerance. *In re Ayers*, 154 F.2d 182, 185 (Fed. Cir. 1946). Similarly, in Johnson and Johnson v. W.L. Gore & Associates, Inc., the Court allowed for "about 1.2" to be inclusive of 1.0. See Johnson and Johnson v. W.L. Gore & Associates, Inc., 436 F.Supp. 704, 728-729 (Fed. Cir. 1977). Although about has never been confined to specific percentage of variability, the Johnson and Johnson decision at least implies that 16% variability is permissible when "about" is used (1.0/1.2 = ~16.6% variability). Thus, the term "about" implicitly discloses some variability even though the specification may not literally cite this variability. Thus, the disclosure of leucine in about 23% encompasses a % of "about" 25%, as claimed. Furthermore, the reference teaches that the liquid nutritional composition comprises per liter (a) at least 0.45 gm (450 mg) of ω-3

fatty acids, (b) at least 50 grams of a source of amino-nitrogen wherein 15-50% by weight of the amino-nitrogen is branched-chain amino acids and wherein tryptophan is present in an amount less than about 5.0% of the total amino-nitrogen, and (c) at least 1 gram of an antioxidant (see column 4, lines 20-36). Therefore, if there was 46% of leucine present, and 46% of 50 gram is 23 grams of leucine present in the composition, this implies that there is about 46% of leucine present in the composition.

The reference further teaches that the composition comprises essential amino acids, such as lysine, isoleucine, methionine, phenylalanine, threonine, tryptophan, valine or histidine, and teaches the amino acid profile of a nutritional composition (see Table 4). Since there is at least about 36 g of essential and/or conditionally essential amino acids per serving and about 15-50 g of BCAA per 100 g of protein, meeting the limitation of claims 14 and 16. Furthermore, since the reference teaches that there is at least 50 grams of a source of amino-nitrogen wherein 15-50% by weight of the amino nitrogen is BCAA, and Table 4 indicates that 9.08 gram of leucine is present, according to the calculation above, this equals about 46% of BCAA. Thus, if 50% by weight of the amino nitrogen is BCAA, there is at least 25 grams of BCAA present. And if about 46% of BCAA is leucine, this implies that there is about 11.5 g of leucine present, meeting the limitation of claim 26. The reference teaches 2.78 g of methionine in 100 g of protein, meeting the limitation of at least about 0.5% to about 5% of methionine of claim 7, The reference teaches that the nutritional composition comprises vitamin E (tocopherol (all natural form or d1-alpha-tocopherol acetate) (see Table 6), meeting the limitation of claim 11. The reference teaches that the EPA is in the amount of 1.09 g and

DHA is in the amount of 0.46 g (see Table 3), meeting the limitation of claims 8-10. The reference further teaches that for treatment of ulcerative colitis, compositions include a protein source that can be intact or hydrolyzed proteins of high biological value (see column 3, lines 1-5) and teaches 75% whey protein concentrate as one of the ingredients (see table 7). Furthermore, since the reference teaches a whey protein concentrate, this protein would inherently comprise essential and conditionally essential amino acid profiled, thus meeting the limitation of range from about 0.60 to about 0.90 amino acids. Furthermore, the reference teaches that for example, the daily nutritional management of liver cancer includes administration of 2 to 4 containers of 8 ounces servings (237 mL) of the nutritional composition providing a daily amount of (i) combined EPA and DHA in the range of 3 to 6 g (preferred dosage 3 g), (ii) BCAA in the range of 5 to 25 g (preferred dosage about 10-15 g), (iii) vitamin C in the range of 125 to 500 mg (preferred about 300 mg), (iv) vitamin E (tocopherol) in the range of 50 to 250 IU (preferred 150 IU), (v) beta-carotene in the range of 1250 to 3250 μg (preferred 2500 μg), (vi) selenium in the range of 40 to 60 μg (preferred about 45 μg). The reference teaches that for cancer cachexia and anorexia, the effect of nutritional intervention are monitored at monthly intervals as known in the art, and depending on the results obtained, the therapeutic regimen is developed to maintain and/or boost the weight gain by the patient (see column 15, lines 44-65, Example III). The mass equivalents of 1 IU for vitamin E is 0.667 mg d-alpha-tocopherol, or of 1 mg of d1-alpha-tocopherol acetate (definition of IU from medicinenet.com). Therefore, 50 to 250 IU would equal to 33.55

mg to 167.75 mg of tocopherol, meeting the limitation of claim 13. Therefore, the reference anticipates claims 1-4, 7-11, 13-14, 16 and 23-26.

Response to Applicant's Arguments

5. Applicant argues that "Applicant has surprisingly found that a formulation containing free essential amino acids as compared to a formulation containing free essential and non-essential amino acids or intact protein alone is optimal. Nutritional compositions comprising a mixture of essential amino acids in free form and/or in salt form that has particularly high amounts of leucine had a stimulatory effect on muscle protein synthesis." Applicant further argues that "Applicant has surprisingly and unexpectedly found that particularly useful compositions for promotion of muscle protein synthesis or controlling tumor-induced weight loss, such as cachexia, may be obtained by combining essential amino acids in free and/or in salt form with intact protein." Applicant further argues that "Abbruzzese fails to disclose or suggest that leucine, in free and/or salt form, is present in an amount of at least 30% by weight based on the weight of intact protein as required by the present independent claims...Abbruzzese further fails to disclose or suggest a ratio of total essential amino acids and optionally, conditionally essential amino acids to total amino acids ranging from about 0.60 to about 0.90." Applicant argues that "Abbruzzese require a lower amount of a source of amino-nitrogen, and will have a lower amount of leucine." Applicant further argues that "the skilled artisan would understand that a composition having about 23% leucine would be entirely distinguishable from a composition having about 30% leucine."

Furthermore, Applicant argues that "the skilled artisan would not arrive at the claimed invention using Abbruzzese in the absence of hindsight because the cited reference fails to recognize the surprising and unexpected benefits of the claimed compositions having optimal amounts of leucine and essential amino acids." Applicant further argues that "in the composition of Abbruzzese, the ratio of total essential amino acids and conditionally essential amino acids to total amino acids is 0.51, which is much lower than that of the present claims."

6. Applicant's arguments have been fully considered but have not been found persuasive. Unexpected results and surprising results do not overcome an anticipatory rejections. The reference teaches all of the active components of instant claims. As described in the body of the rejection, the reference teaches a liquid nutritional composition comprising (a) at least 1000 mg per liter of ω-3 fatty acids, wherein the weight ratio of ω-6 fatty acids to ω-3 fatty acids is from about 0.1 to about 1.0; (b) at least 50 grams per liter of a source of amino nitrogen, wherein 15 to 50% by weight of the amino-nitrogen is branched-chain amino acids, and wherein tryptophan is present in an amount less than about 5.0% by weight of the total amino -nitrogen, and (c) at least 1 gram per liter of an antioxidant system comprising beta-carotene, vitamin C, vitamin E and selenium (see claim 1). The reference teaches that the total amount of branched-chain amino acids ("BCAA") useful in the present invention is about 15-50 g/100 g protein (i.e. percent), preferably about 15-25 g/100 g. The reference teaches that the daily delivery of BCAAs is about 5-26 g (see column 9, lines 26-31). The reference teaches the branched-chain amino acids valine, leucine, isoleucine or mixtures thereof

(see abstract). Since there is 9.08 g of leucine and total of 19.75 g of BCAA, 9.08/19.75 is about 46% of the leucine in the BCAA. Since the reference teaches that the total amount of BCAA useful in the present invention is about 15-50 g/100 g protein, and there is 46% of leucine in the BCAA composition, this implies that there is at least about 23% of leucine.

Example 1 of the instant specification discloses the non-essential amino acids synthesized within the body at a rate sufficient to provide daily requirements, needed for an amino acid mixture to stimulate muscle protein synthesis. Table 1 shows that 3.2 g of leucine was given out of total essential amino acids of 18.2 g. This is about 17.6% leucine. Within the balanced amino acids, 3.2 g out of 40.1 g of total amino acids equals to about 8% of leucine. Example 2 indicates that ingestion of essential amino acids (EAAs) is more effective than ingestion of a comparable amount of intact protein in stimulating net muscle protein synthesis in unstressed elderly individuals. Example 3 describes the optimal mixture of free amino acids for stimulating net muscle protein synthesis. Table 2 shows amino acid composition in 100 ml of the infusion solutions. Table 3 shows the leucine infusion. Table 4 shows the results of protein synthesis, breakdown and net balance of the leucine infusion and the amino acid compositions of Tables 2 and 3. Table 4 shows that with control, there was 5.4 ± 0.6 protein synthesis, 9.2 ± 1.1 protein breakdown and a net balance of -3.8 ± 0.5. For Leu 25%, there was 6.8 ± 1.1, 8.1 ± 1.2 and net balance of -1.2 ± 0.2; For Leu 35%, there was 6.9 ± 0.6 protein synthesis, 8.0 ± 0.4 breakdown, net balance of -1.0 ± 0.4; For leucine alone, there was 6.6 ± 0.7 protein synthesis, 9.2 ± 0.5 breakdown, and bet balance of -2.6 ±

0.3. All of the leucine results, leucine alone (no percentage given), leucine (25%), leucine (35%), are about the same in regards to synthesis, breakdown and net balance. For example, For 25% leucine, the net balance is -1.3 ± 1.1 (Examiner's calculation); for 35% leucine, the net balance is -1.1 ± 0.5; for leucine alone, the net balance is -2.6 ± 0.6. Therefore, by looking at the instant specification and the results, the artisan would have expected Leu to behave the same at 25 or 30 or 35%. Applicant's own example 4 shows clearly that Leu does not improve muscle building, so at different concentrations of Leu would function the same. Therefore, the reference teachings at least 23% Leu would be expected to behave the same, therefore, at least about 23% still anticipates at least about 30% of leucine. Furthermore, since there is 75% whey protein concentrate as one of the ingredients (see table 7), this protein would inherently comprise essential and conditionally essential amino acid profiled, thus meeting the limitation of range from about 0.60 to about 0.90 amino acids. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, Applicant is reminded that the rejection is under 35 U.S.C. 102(b). Therefore, this argument does not apply to this rejection. Therefore, the reference anticipates instant claims 1-4, 7-11, 12-14, 16 and 23-26.

7. Claims 1-4, 7-11, 13-14, 16 and 23-26 remain rejected under 35 U.S.C. 102(a) as being anticipated by Abbruzzese et al (US Patent No. 6,387,883).

8. Abbruzzese et al teach nutritional compositions for the prevention of cachexia and anorexia. The reference teaches a composition comprising effective amounts of ω-3

fatty acids, such as alpha-linolenic acid, stearidonic acid, eicosapentanenoic acid, docosapentaenoic acid, docosahexanoic acid or mixtures thereof; of branched-chain amino acids valine, leucine, isoleucine or mixtures thereof; with or without reduced levels of tryptophan and 5-hydroxytryptophan; and of antioxidant system selected from the group consisting of beta-carotene, vitamin C, vitamin E, selenium or mixtures thereof (see abstract). The reference teaches a liquid nutritional composition comprising (a) at least 450 mg per liter of ω-3 fatty acids, wherein the weight ratio of ω-6 fatty acids to ω-3 fatty acids is from about 0.1 to about 1.0, and (b) an antioxidant system comprising at least one ingredient selected from the group consisting of beta-carotene, vitamin C, vitamin E and selenium (see claim 1). The reference further teaches a composition further comprising at least 50 grams per liter of a source of amino acid nitrogen, in which 15% to 50% by weigh of the amino acids of said source of amino acid nitrogen are BCAA which are present in a peptide, a protein, or as free amino acids, and selected from valine, leucine, and isoleucine (see claims 5-7). The reference teaches that the total amount of branched-chain amino acids ("BCAA") useful in the present invention is about 15-50 g/100 g protein (i.e. percent), preferably about 15-25 g/100 g. Thus, an 8 oz container of the nutritional composition would contain up to about 8 g BCAAs per 16 grams of total protein. The daily delivery of BCAAs is about 5-26 g (see column 9, lines 26-31). The reference teaches the branched-chain amino acids valine, leucine, isoleucine or mixtures thereof (see abstract). Therefore, since there is 9.08 g and total of 19.75 g of BCAA, 9.08/19.75 is about 46% of the leucine in the BCAA. Since the reference teaches that the total amount of BCAA useful in the

present invention is about 15-50 g/100 g protein, and there is 46% of leucine in the BCAA composition, this implies that there is at least about 23% of leucine. Additionally, the reference teaches that the nutritional compositions comprises branched-chain amino acids, valine, leucine, isoleucine or mixtures of thereof. It is noted that claims 1-2 have been rejected over the prior art, even though the reference does not disclose exact % range as claimed. However, both the claims and the reference utilize the term "about" when discussing the amount of leucine (branched-chain amino acid). It is The term "about" allows for some tolerance in the ranges disclosed. In *In re Ayers*, the Federal Circuit held that "at least about 10%" was anticipated by a reference that disclosed "about 8%" because the term "about" allowed for some tolerance. *In re Ayers*, 154 F.2d 182, 185 (Fed. Cir. 1946). Similarly, in Johnson and Johnson v. W.L. Gore & Associates, Inc., the Court allowed for "about 1.2" to be inclusive of 1.0. See Johnson and Johnson v. W.L. Gore & Associates, Inc., 436 F.Supp. 704, 728-729 (Fed. Cir. 1977). Although about has never been confined to specific percentage of variability, the Johnson and Johnson decision at least implies that 16% variability is permissible when "about" is used (1.0/1.2 = ~16.6% variability). Thus, the term "about" implicitly discloses some variability even though the specification may not literally cite this variability. Thus, the disclosure of leucine in about 23% encompasses a % of "about" 25%, as claimed. Furthermore, the reference teaches that the liquid nutritional composition comprises per liter (a) at least 0.45 gm (450 mg) of ω-3 fatty acids, (b) at least 50 grams of a source of amino-nitrogen wherein 15-50% by weight of the amino-nitrogen is branched-chain amino acids and wherein tryptophan is present in an amount

less than about 5.0% of the total amino-nitrogen, and (c) at least 1 gram of an antioxidant (see column 4, lines 20-36). Therefore, if there was 46% of leucine present, and 46% of 50 gram is 23 grams of leucine present in the composition, this implies that there is about 46% of leucine present in the composition.

The reference further teaches that the composition comprises essential amino acids, such as lysine, isoleucine, methionine, phenylalanine, threonine, tryptophan, valine or histidine (see Table 4). Since there is at least about 36 g of essential and/or conditionally essential amino acids per serving and about 15-50 g of BCAA per 100 g of protein, meeting the limitation of claims 14 and 16. Furthermore, since the reference teaches that there is at least 50 grams of a source of amino-nitrogen wherein 15-50% by weight of the amino nitrogen is BCAA, and Table 4 indicates that 9.08 gram of leucine is present, according to the calculation above, this equals about 46% of BCAA. Thus, if 50% by weight of the amino nitrogen is BCAA, there is at least 25 grams of BCAA present. And if about 46% of BCAA is leucine, this implies that there is about 11.5 g of leucine present, meeting the limitation of claim 26. The reference teaches 2.78 g of methionine in 100 g of protein, meeting the limitation of at least about 0.5% to about 5% of methionine of claim 7, The reference teaches that the nutritional composition comprises vitamin E (tocopherol (all natural form or d1-alpha-tocopherol acetate) (see Table 6), meeting the limitation of claim 11. The reference teaches that the EPA is in the amount of 1.09 g and DHA is in the amount of 0.46 g (see Table 3), meeting the limitation of claims 8-10. The reference further teaches that for treatment of ulcerative colitis, compositions include a protein source that can be intact or hydrolyzed proteins of

high biological value (see column 3, lines 1-5) and teaches 75% whey protein concentrate as one of the ingredients (see table 7). Furthermore, since the reference teaches a whey protein concentrate, this protein would inherently comprise essential and conditionally essential amino acid profiled, thus meeting the limitation of range from about 0.60 to about 0.90 amino acids. Furthermore, the reference teaches that for example, the daily nutritional management of liver cancer includes administration of 2 to 4 containers of 8 ounces servings (237 mL) of the nutritional composition providing a daily amount of (i) combined EPA and DHA in the range of 3 to 6 g (preferred dosage 3 g), (ii) BCAA in the range of 5 to 25 g (preferred dosage about 10-15 g), (iii) vitamin C in the range of 125 to 500 mg (preferred about 300 mg), (iv) vitamin E (tocopherol) in the range of 50 to 250 IU (preferred 150 IU), (v) beta-carotene in the range of 1250 to 3250 μg (preferred 2500 μg), (vi) selenium in the range of 40 to 60 μg (preferred about 45 μg). The reference teaches that for cancer cachexia and anorexia, the effect of nutritional intervention are monitored at monthly intervals as known in the art, and depending on the results obtained, the therapeutic regimen is developed to maintain and/or boost the weight gain by the patient (see column 15, lines 44-65, Example III). The mass equivalents of 1 IU for vitamin E is 0.671 mg d-alpha-tocopherol, or of 1 mg of d1-alpha-tocopherol acetate (definition of IU from medicinenet.com). Therefore, 50 to 250 IU would equal to 33.55 mg to 167.75 mg of tocopherol, meeting the limitation of claim 13. Therefore, the reference anticipates claims 1-4, 7-11, 13-14, 16 and 23-26.

9. Claims 1-4, 7-11, 13-14, 16 and 23-26 remain rejected under 35 U.S.C. 102(e) as being anticipated by Abbruzzese et al (US Patent No. 6,387,883).

10. The teachings of Abbruzzese et al are described, *supra*. Therefore, the reference anticipates claims 1-4, 7-11, 13-14, 16 and 23-26.

Response to Applicant's Arguments

11. Applicant argues that "Applicant has surprisingly found that a formulation containing free essential amino acids as compared to a formulation containing free essential and non-essential amino acids or intact protein alone is optimal. Nutritional compositions comprising a mixture of essential amino acids in free form and/or in salt form that has particularly high amounts of leucine had a stimulatory effect on muscle protein synthesis." Applicant further argues that "Applicant has surprisingly and unexpectedly found that particularly useful compositions for promotion of muscle protein synthesis or controlling tumor-induced weight loss, such as cachexia, may be obtained by combining essential amino acids in free and/or in salt form with intact protein." Applicant further argues that "Abbruzzese fails to disclose or suggest that leucine, in free and/or salt form, is present in an amount of at least 30% by weight based on the weight of intact protein as required by the present independent claims...Abbruzzese further fails to disclose or suggest a ratio of total essential amino acids and optionally, conditionally essential amino acids to total amino acids ranging from about 0.60 to about 0.90." Applicant argues that "Abbruzzese require a lower amount of a source of amino-nitrogen, and will have a lower amount of leucine." Applicant further argues that

"the skilled artisan would understand that a composition having about 23% leucine would be entirely distinguishable from a composition having about 30% leucine." Furthermore, Applicant argues that "the skilled artisan would not arrive at the claimed invention using Abbruzzese in the absence of hindsight because the cited reference fails to recognize the surprising and unexpected benefits of the claimed compositions having optimal amounts of leucine and essential amino acids." Applicant further argues that "in the composition of Abbruzzese, the ratio of total essential amino acids and conditionally essential amino acids to total amino acids is 0.51, which is much lower than that of the present claims."

12. Applicant's arguments have been fully considered but have not been found persuasive. Unexpected results and surprising results do not overcome an anticipatory rejections. The reference teaches all of the active components of instant claims. As described in the body of the rejection, the reference teaches a liquid nutritional composition comprising (a) at least 1000 mg per liter of ω-3 fatty acids, wherein the weight ratio of ω-6 fatty acids to ω-3 fatty acids is from about 0.1 to about 1.0; (b) at least 50 grams per liter of a source of amino nitrogen, wherein 15 to 50% by weight of the amino-nitrogen is branched-chain amino acids, and wherein tryptophan is present in an amount less than about 5.0% by weight of the total amino -nitrogen, and (c) at least 1 gram per liter of an antioxidant system comprising beta-carotene, vitamin C, vitamin E and selenium (see claim 1). The reference teaches that the total amount of branched-chain amino acids ("BCAA") useful in the present invention is about 15-50 g/100 g protein (i.e. percent), preferably about 15-25 g/100 g. The reference teaches that the

daily delivery of BCAAs is about 5-26 g (see column 9, lines 26-31). The reference teaches the branched-chain amino acids valine, leucine, isoleucine or mixtures thereof (see abstract). Since there is 9.08 g of leucine and total of 19.75 g of BCAA, 9.08/19.75 is about 46% of the leucine in the BCAA. Since the reference teaches that the total amount of BCAA useful in the present invention is about 15-50 g/100 g protein, and there is 46% of leucine in the BCAA composition, this implies that there is at least about 23% of leucine.

Example 1 of the instant specification discloses the non-essential amino acids synthesized within the body at a rate sufficient to provide daily requirements, needed for an amino acid mixture to stimulate muscle protein synthesis. Table 1 shows that 3.2 g of leucine was given out of total essential amino acids of 18.2 g. This is about 17.6% leucine. Within the balanced amino acids, 3.2 g out of 40.1 g of total amino acids equals to about 8% of leucine. Example 2 indicates that ingestion of essential amino acids (EAAs) is more effective than ingestion of a comparable amount of intact protein in stimulating net muscle protein synthesis in unstressed elderly individuals. Example 3 describes the optimal mixture of free amino acids for stimulating net muscle protein synthesis. Table 2 shows amino acid composition in 100 ml of the infusion solutions. Table 3 shows the leucine infusion. Table 4 shows the results of protein synthesis, breakdown and net balance of the leucine infusion and the amino acid compositions of Tables 2 and 3. Table 4 shows that with control, there was 5.4 ± 0.6 protein synthesis, 9.2 ± 1.1 protein breakdown and a net balance of -3.8 ± 0.5. For Leu 25%, there was 6.8 ± 1.1, 8.1 ± 1.2 and net balance of -1.2 ± 0.2; For Leu 35%, there was 6.9 ± 0.6

protein synthesis, 8.0 ± 0.4 breakdown, net balance of -1.0 ± 0.4; For leucine alone, there was 6.6 ± 0.7 protein synthesis, 9.2 ± 0.5 breakdown, and bet balance of -2.6 ± 0.3. All of the leucine results, leucine alone (no percentage given), leucine (25%), leucine (35%), are about the same in regards to synthesis, breakdown and net balance. For example, For 25% leucine, the net balance is -1.3 ± 1.1 (Examiner's calculation); for 35% leucine, the net balance is -1.1 ± 0.5; for leucine alone, the net balance is -2.6 ± 0.6. Therefore, by looking at the instant specification and the results, the artisan would have expected Leu to behave the same at 25 or 30 or 35%. Applicant's own example 4 shows clearly that Leu does not improve muscle building, so at different concentrations of Leu would function the same. Therefore, the reference teachings at least 23% Leu would be expected to behave the same, therefore, at least about 23% still anticipates at least about 30% of leucine. Therefore, by looking at the instant specification and the results, the artisan would have expected Leu to behave the same at 25 or 30 or 35%. Applicant's own example 4 shows clearly that Leu does not improve muscle building, so at different concentrations of Leu would function the same. Therefore, the reference teachings at least 23% Leu would be expected to behave the same, therefore, at least about 23% still anticipates at least about 30% of leucine. Furthermore, since there is 75% whey protein concentrate as one of the ingredients (see table 7), this protein would inherently comprise essential and conditionally essential amino acid profiled, thus meeting the limitation of range from about 0.60 to about 0.90 amino acids. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, Applicant is reminded that the rejection is under 35

U.S.C. 102(a) and 102(e). Therefore, this argument does not apply to this rejection.

Therefore, the reference anticipates instant claims 1-4, 7-11, 13-14, 16 and 23-26.

35 U.S.C. 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

For the purpose of this invention, the level of ordinary skill in the art is deemed to be at least that level of skill demonstrated by the patents in the relevant art. Joy Technologies Inc. V. Quigg, 14 USPQ2d 1432 (DC DC 1990). One of ordinary skill in the art is held in accountable not only for specific teachings of references, but also for inferences which those skilled in the art may reasonably be expected to draw. *In re Hoeschele*, 160 USPQ 809, 811 (CCPA 1969). In addition, one of ordinary skill in the art is motivated by economics to depart from the prior art to reduce costs consistent with desired product properties. *In re Clinton*, 188 USPQ 365, 367 (CCPA 1976);*In re Thompson*, 192 USPQ 275, 277 (CCPA 1976).

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 1-4, 7-11, 13-14, 16-17 and 23-28 remain rejected under 35 U.S.C. 103(a) as unpatentable over Abbruzzese et al (US Patent No. 6,077,828) in view of Hageman et al (US Patent No. 6,420,342) and Salvati et al (US Patent No. 6,953,679).

16. The teachings of Abbruzzese are described, *supra*. The difference between the reference and the instant claims is that the reference does not teach a kit comprising a first composition and a second composition comprising an anti-cancer drug, wherein said anticancer drug is 5-fluorouracil, mitomycin-C, adriamycin, chloroethyl nitrosureas or methotrexate, and that the methionine in free and/or salt from is in an amount of at least about 5% to about 7% by weight on the weight of total amino acids.

17. However, Hageman et al teach a nutritional, pharmaceutical or dietetic preparation can be manufacture in dry form, as bar, as powder, as tablet, and cookie or as cereal (see column 5, lines 60-63). The reference teaches for products for sportsmen the following mixtures of amino acids appeared to be especially beneficial for muscle growth, when consumed in an amount of more than 2 and preferably more than 4 g per daily dose: 3-10 wt% histidine, 5-15% isoleucine, 10-23% % leucine, 10-23% lysine, 5-15% methionine, 5-15 wt % phenylalanine, and 5-15 wt % threonine (see column 6, lines 59-67 and column 7, line 1). Furthermore, the reference teaches that when proteins are included in the nutritional preparations, the amount that is included

depends on the application (see column 6, lines 39-41) and the proteins are proteins of dairy, vegetable or animal origin, such as skimmed milk powder, whey powder, egg white powder, potato protein, soy protein, etc., or hydrolysates, or mixtures thereof (see column 6, lines 27-32). The reference teaches that when proteins are included in the nutritional preparation, the amount that is included depends on the application of the product. In complete formula typically an amount of 5-120 g per daily dose…for young infants the amount will be in the range 5-15 g per daily dose...in complete enteral nutrition for feeding surgery patients, typically 50-120 g per daily dose…In supplement typically 0-60 g protein per daily dose will be included (see column 6, lines 39-50). In regards to claim 25, the claim is drawn to "a composition consisting essentially of..." In regards to claim 27, the claim is drawn to "a kit comprising: a first composition consisting essentially of..." Applicant has not defined what encompasses "consisting essentially of" in the specification. In fact the instant specification does not define the phrase "consisting essentially of". The MPEP states the following: "The transitional phrase 'consisting essentially of' limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. A 'consisting essentially of' claim occupies the middle ground between closed claims that are written in a consisting of' format and fully open claims that are drafted in a comprising' format...For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to 'comprising'" (see MPEP 2105). Therefore, claims

25 and 28 have been treated as "a composition comprising..." the same claim language as original claim 3.

18. Furthermore, Salvati et al teach a fused cyclic compound and the use of the fused cyclic compound with a nutritional supplements in combination with whey protein or casein, amino acids (such as leucine, branched amino acid and hydroxymethylbutyrate), triglycerides, vitamins (e.g., A, B6, B12, folate, C, D, and E), minerals, etc (see column 45, lines 48-56). Furthermore, the reference teaches anti-proliferative agents for use in combination with the compounds such as adriamycin (see column 45, lines 41-43) and anti-cancer agents, such as methotrexate, 5-fluorouracil (see column 46, lines 64-67). The reference teaches a kit comprising a first container (such as a vial) containing a pharmaceutical formulation comprising a compound, a second container (such as a vial) containing a pharmaceutical formulation comprising one or more agents to be used in combination with the compound of the invention (see 47, lines 55-64).

19. Therefore, it would have been obvious for one of ordinary skill in the art to combine the teachings of Abbruzzese et al, Hageman et al and Salvati et al to produce a kit comprising the anti-cancer agent with the nutritional composition, since all of the prior art teach nutritional composition. Salvati et al teach a kit comprising fused cyclic compound, nutritional supplement comprising leucine, whey and protein and any anti-cancer agent and Hageman et al and Abburuzzese et al teach a nutritional composition comprising different amounts of amino acids. One of ordinary skill in the art would be motivated to combine, since Salvati et al teaches such a composition/kit. Furthermore,

the composition taught in Abbruzzese, Hageman, and Salvati can be used for the same purpose, for administering nutritional composition for such patients as cancer patients. As evidenced by the instant specification, the compositions of the instant application are for the promotion of muscle protein synthesis and control of tumor-induced weight loss in patients that are, for example, suffering from cancer cachexia (see abstract). Furthermore, one of ordinary skill in the art would have been motivated to optimize the concentrations of the methionine, since "it is the normal desire of scientist or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is optimum combination of percentages". The MPEP states: Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. *"[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)* (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("*The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); In re Hoeschele, 406*

F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). Furthermore, Abbruzzese patent '828 teaches that the effect of nutritional intervention on cancer cachexia and anorexia are monitored as known in the art, and depending on the results obtained, the therapeutic regimen is developed to maintain and /or boost weight gain by the patient, with the ultimate goal of achieving tumor regression and complete eradication of cancer cells (see column 15, lines 57-64). Therefore, there is a reasonable expectation of success to optimize the concentrations of the essential amino acid/ methionine, since it is "the normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages" and one of ordinary skill in the art would experiment with different concentrations to produce the optimal product. Due to the loss of appetite due to cancer treatment, and due to appetite suppression, nutrition is necessarily a part of treatment process for improving patient's everyday life. For the process of improving and treating cancer and loss of appetite due to cancer, a nutritional requirement would be optimized and adjusted accordingly by those skilled in the art. Abbruzzese teaches that the

therapeutic regimen will be developed to maintain and/or boost weight gain, giving motivation to optimize the nutritional content. From the teachings of the references, it is apparent that one of the ordinary skills in the art would have had a reasonable expectation of success in producing the claimed invention. Thus, the invention as a whole is *prima facie* obvious over the references, especially in the absence of evidence to the contrary. There is a reasonable expectation of success, since Salvati et al teach a kit that can comprise any agent, nutritional supplement for the treatment of cancer (prostate), and Hageman et al and Abbruzzese et al teach a nutritional supplement comprising essential amino acids that is useful in treating variety of diseases, including cancer.

Response to Applicant's Arguments

20. Applicant argues that "Hageman and Salvati fail to remedy the deficiencies of Abbruzzese. Hageman and Salvati fail to disclose or suggest leucine, in free and/or salt form, is present in an amount of at least 30% by weight based on the weight of intact protein as required by the present claims....fail to disclose or suggest a ratio of total essential amino acids and, optionally, conditionally essential amino acids to total amino acids ranging from about 0.60 to about 0.90 as required by independent claims 3, 17, 25 and 28." Applicant further argues that "the skilled artisan would not arrive at the claimed invention using Hageman and Salvati in the absence of hindsight because the cited references are entirely directed to compositions utilizing different nutritional ingredients for different intended purposes. Moreover, Hageman and Salvati fail to even recognize the surprising and unexpected benefits of the claimed compositions having

optimal amounts of leucine and essential amino acids." Applicant argues that "there is absolutely no guidance in Hageman and Salvati for one of skill in the art to choose the active components and effective amount of the components present in the instant claims to achieve the unexpected improved composition as Applicant has done."

21. Applicant's arguments have been fully considered but have not been found persuasive. The primary reference teaches all of the active components of instant claims. As described in the body of the rejection, the reference teaches a liquid nutritional composition comprising (a) at least 1000 mg per liter of ω-3 fatty acids, wherein the weight ratio of ω-6 fatty acids to ω-3 fatty acids is from about 0.1 to about 1.0; (b) at least 50 grams per liter of a source of amino nitrogen, wherein 15 to 50% by weight of the amino-nitrogen is branched-chain amino acids, and wherein tryptophan is present in an amount less than about 5.0% by weight of the total amino -nitrogen, and (c) at least 1 gram per liter of an antioxidant system comprising beta-carotene, vitamin C, vitamin E and selenium (see claim 1). The reference teaches that the total amount of branched-chain amino acids ("BCAA") useful in the present invention is about 15-50 g/100 g protein (i.e. percent), preferably about 15-25 g/100 g. The reference teaches that the daily delivery of BCAAs is about 5-26 g (see column 9, lines 26-31). The reference teaches the branched-chain amino acids valine, leucine, isoleucine or mixtures thereof (see abstract). Since there is 9.08 g of leucine and total of 19.75 g of BCAA, 9.08/19.75 is about 46% of the leucine in the BCAA. Since the reference teaches that the total amount of BCAA useful in the present invention is about 15-50

g/100 g protein, and there is 46% of leucine in the BCAA composition, this implies that there is at least about 23% of leucine.

Hageman et al teach a nutritional, pharmaceutical or dietetic preparation can be manufacture in dry form, as bar, as powder, as tablet, and cookie or as cereal (see column 5, lines 60-63). The reference teaches for products for sportsmen the following mixtures of amino acids appeared to be especially beneficial for muscle growth, when consumed in an amount of more than 2 and preferably more than 4 g per daily dose: 3-10 wt% histidine, 5-15% isoleucine, 10-23% % leucine, 10-23% lysine, 5-15% methionine, 5-15 wt % phenylalanine, and 5-15 wt % threonine (see column 6, lines 59-67 and column 7, line 1). Furthermore, Salvati et al teach a fused cyclic compound and the use of the fused cyclic compound with a nutritional supplements in combination with whey protein or casein, amino acids (such as leucine, branched amino acid and hydroxymethylbutyrate), triglycerides, vitamins (e.g., A, B6, B12, folate, C, D, and E), minerals, etc (see column 45, lines 48-56). Furthermore, the reference teaches anti-proliferative agents for use in combination with the compounds such as adriamycin (see column 45, lines 41-43) and anti-cancer agents, such as methotrexate, 5-fluorouracil (see column 46, lines 64-67). The reference teaches a kit comprising a first container (such as a vial) containing a pharmaceutical formulation comprising a compound, a second container (such as a vial) containing a pharmaceutical formulation comprising one or more agents to be used in combination with the compound of the invention (see 47, lines 55-64).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings because all references teach nutritional compositions comprising differing amounts of protein and essential amino acids (such as leucine) for the same purpose (muscle enhancement). Salvati reference teaches combining antiproliferative agents for use in combination with the compounds and a kit containing the pharmaceutical formulation. Furthermore, the composition taught in Abbruzzese, Hageman, and Salvati can be used for the same purpose, for administering nutritional composition for such patients as cancer patients. As evidenced by the instant specification, the compositions of the instant application are for the promotion of muscle protein synthesis and control of tumor-induced weight loss in patients that are, for example, suffering from cancer cachexia (see abstract). Due to the loss of appetite due to cancer treatment, and due to appetite suppression, nutrition is necessarily a part of treatment process for improving patient's everyday life. For the process of improving and treating cancer and loss of appetite due to cancer, a nutritional requirement would be optimized and adjusted accordingly by those skilled in the art. Abbruzzese teaches that the therapeutic regimen will be developed to maintain and/or boost weight gain, giving motivation to optimize the nutritional content. From the teachings of the references, it is apparent that one of the ordinary skills in the art would have had a reasonable expectation of success in producing the claimed invention. Thus, the invention as a whole is *prima facie* obvious over the references, especially in the absence of evidence to the contrary. There is a reasonable expectation of success, since Salvati et al teach a kit that can comprise any agent, nutritional supplement for the treatment of cancer (prostate), and Hageman et al

and Abbruzzese et al teach a nutritional supplement comprising essential amino acids that is useful in treating variety of diseases, including cancer.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

New Rejection

35 U.S.C. 112, second paragraph

22. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

23. Claims 10, 13-14, 16 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

24. Claim 10 recites, "...at least about 1 g of eicosapentaenoic acid per serving or at least about 2 g of eicosapentaenoic acid per daily dose." It is unclear how one can quantify the amount of a component in a daily dose.

25. Claim 13 recites, "...tocopherol is present in an amount about 50 mg per serving or at least 150 mg per daily dose." It is unclear how one can quantify the amount of a component in a daily dose.

26. Claim 14 recites, "...from about 15 g to about 55 g amino acids in free and/or salt form per daily dose." It is unclear how one can quantify the amount of a component in a daily dose.

27. Claim 16 recites, "...from about 36 g to about 72 g total essential and/or conditionally essential amino acids per serving." It is unclear how one can quantify the amount of a component per serving. Furthermore, serving basically requires instructions on how much to give, and that is more "method" language, and not a composition.

28. Claim 26 recites, "...from about 12 g to about 15 g leucine in free and/or salt form per daily dose." It is unclear how one can quantify the amount of a component in a daily dose.

35 U.S.C. 103

29. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

For the purpose of this invention, the level of ordinary skill in the art is deemed to be at least that level of skill demonstrated by the patents in the relevant art. Joy Technologies Inc. V. Quigg, 14 USPQ2d 1432 (DC DC 1990). One of ordinary skill in the art is held in accountable not only for specific teachings of references, but also for inferences which those skilled in the art may reasonably be expected to draw. *In re Hoeschele*, 160 USPQ 809, 811 (CCPA 1969). In addition, one of ordinary skill in the art is motivated by economics to depart from the prior art to reduce costs consistent with desired product properties. *In re Clinton*, 188 USPQ 365, 367 (CCPA 1976);*In re Thompson*, 192 USPQ 275, 277 (CCPA 1976).

30. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

31. Claims 1-4, 7-11, 13-14, 16 and 23-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Abbruzzese et al (US Patent No. 6,077,828, filed with IDS) in view of Allen et al (US 2003/0119888 A1) and Phillips Bill (Sports Supplement Review, 1997, pp. 66-70).

32. Abbruzzese et al teach nutritional compositions for the prevention of cachexia and anorexia. The reference teaches a composition comprising effective amounts of ω-3 fatty acids, such as alpha-linolenic acid, stearidonic acid, eicosapentanenoic acid,

docosapentaenoic acid, docosahexanoic acid or mixtures thereof; of branched-chain amino acids valine, leucine, isoleucine or mixtures thereof; with or without reduced levels of tryptophan and 5-hydroxytryptophan; and of antioxidant system selected from the group consisting of beta-carotene, vitamin C, vitamin E, selenium or mixtures thereof (see abstract). The reference teaches a liquid nutritional composition comprising (a) at least 1000 mg per liter of ω-3 fatty acids, wherein the weight ratio of ω-6 fatty acids to ω-3 fatty acids is from about 0.1 to about 1.0; (b) at least 50 grams per liter of a source of amino nitrogen, wherein 15 to 50% by weight of the amino-nitrogen is branched-chain amino acids, and wherein tryptophan is present in an amount less than about 5.0% by weight of the total amino -nitrogen, and (c) at least 1 gram per liter of an antioxidant system comprising beta-carotene, vitamin C, vitamin E and selenium (see claim 1). The reference teaches that the total amount of branched-chain amino acids ("BCAA") useful in the present invention is about 15-50 g/100 g protein (i.e. percent), preferably about 15-25 g/100 g. Thus, an 8 oz container of the nutritional composition would contain up to about 8 g BCAAs per 16 grams of total protein. The daily delivery of BCAAs is about 5-26 g (see column 9, lines 26-31). The reference teaches the branched-chain amino acids valine, leucine, isoleucine or mixtures thereof (see abstract). Therefore, since there is 9.08 g and total of 19.75 g of BCAA, 9.08/19.75 is about 46% of the leucine in the BCAA. Since the reference teaches that the total amount of BCAA useful in the present invention is about 15-50 g/100 g protein, and there is 46% of leucine in the BCAA composition, this implies that there is at least about 23% of leucine. Additionally, the reference teaches that the nutritional compositions

comprises branched-chain amino acids, valine, leucine, isoleucine or mixtures of thereof. It is noted that claims 1-2 have been rejected over the prior art, even though the reference does not disclose exact % range as claimed. However, both the claims and the reference utilize the term "about" when discussing the amount of leucine (branched-chain amino acid). It is the term "about" allows for some tolerance in the ranges disclosed. In *In re Ayers*, the Federal Circuit held that "at least about 10%" was anticipated by a reference that disclosed "about 8%" because the term "about" allowed for some tolerance. *In re Ayers*, 154 F.2d 182, 185 (Fed. Cir. 1946). Similarly, in Johnson and Johnson v. W.L. Gore & Associates, Inc., the Court allowed for "about 1.2" to be inclusive of 1.0. See Johnson and Johnson v. W.L. Gore & Associates, Inc., 436 F.Supp. 704, 728-729 (Fed. Cir. 1977). Although about has never been confined to specific percentage of variability, the Johnson and Johnson decision at least implies that 16% variability is permissible when "about" is used (1.0/1.2 = ~16.6% variability). Thus, the term "about" implicitly discloses some variability even though the specification may not literally cite this variability. Thus, the disclosure of leucine in about 23% encompasses a % of "about" 25%, as claimed. Furthermore, the reference teaches that the liquid nutritional composition comprises per liter (a) at least 0.45 gm (450 mg) of ω-3 fatty acids, (b) at least 50 grams of a source of amino-nitrogen wherein 15-50% by weight of the amino-nitrogen is branched-chain amino acids and wherein tryptophan is present in an amount less than about 5.0% of the total amino-nitrogen, and (c) at least 1 gram of an antioxidant (see column 4, lines 20-36). Therefore, if there was 46% of

leucine present, and 46% of 50 gram is 23 grams of leucine present in the composition, this implies that there is about 46% of leucine present in the composition.

The reference further teaches that the composition comprises essential amino acids, such as lysine, isoleucine, methionine, phenylalanine, threonine, tryptophan, valine or histidine, and teaches the amino acid profile of a nutritional composition (see Table 4). Since there is at least about 36 g of essential and/or conditionally essential amino acids per serving and about 15-50 g of BCAA per 100 g of protein, meeting the limitation of claims 14 and 16. Furthermore, since the reference teaches that there is at least 50 grams of a source of amino-nitrogen wherein 15-50% by weight of the amino nitrogen is BCAA, and Table 4 indicates that 9.08 gram of leucine is present, according to the calculation above, this equals about 46% of BCAA. Thus, if 50% by weight of the amino nitrogen is BCAA, there is at least 25 grams of BCAA present. And if about 46% of BCAA is leucine, this implies that there is about 11.5 g of leucine present, meeting the limitation of claim 26. The reference teaches 2.78 g of methionine in 100 g of protein, meeting the limitation of at least about 0.5% to about 5% of methionine of claim 7, The reference teaches that the nutritional composition comprises vitamin E (tocopherol (all natural form or d1-alpha-tocopherol acetate) (see Table 6), meeting the limitation of claim 11. The reference teaches that the EPA is in the amount of 1.09 g and DHA is in the amount of 0.46 g (see Table 3), meeting the limitation of claims 8-10. The reference further teaches that for treatment of ulcerative colitis, compositions include a protein source that can be intact or hydrolyzed proteins of high biological value (see column 3, lines 1-5) and teaches 75% whey protein concentrate as one of the ingredients (see

table 7). Furthermore, since the reference teaches a whey protein concentrate, this protein would inherently comprise essential and conditionally essential amino acid profiled, thus meeting the limitation of range from about 0.60 to about 0.90 amino acids. Furthermore, the reference teaches that for example, the daily nutritional management of liver cancer includes administration of 2 to 4 containers of 8 ounces servings (237 mL) of the nutritional composition providing a daily amount of (i) combined EPA and DHA in the range of 3 to 6 g (preferred dosage 3 g), (ii) BCAA in the range of 5 to 25 g (preferred dosage about 10-15 g), (iii) vitamin C in the range of 125 to 500 mg (preferred about 300 mg), (iv) vitamin E (tocopherol) in the range of 50 to 250 IU (preferred 150 IU), (v) beta-carotene in the range of 1250 to 3250 μg (preferred 2500 μg), (vi) selenium in the range of 40 to 60 μg (preferred about 45 μg). The reference teaches that for cancer cachexia and anorexia, the effect of nutritional intervention are monitored at monthly intervals as known in the art, and depending on the results obtained, the therapeutic regimen is developed to maintain and/or boost the weight gain by the patient (see column 15, lines 44-65, Example III). The mass equivalents of 1 IU for vitamin E is 0.667 mg d-alpha-tocopherol, or of 1 mg of d1-alpha-tocopherol acetate (definition of IU from medicinenet.com). Therefore, 50 to 250 IU would equal to 33.55 mg to 167.75 mg of tocopherol, meeting the limitation of claim 13. The difference between the reference and the instant claims is that the reference does not teach greater than 30% to about 95% by weight of leucine.

33. However, Allen teaches that maintaining muscle mass while minimizing the accumulation of fat has long been an issue of concern to athletes. Food and/or vitamin

supplements, as well as pituitary growth hormone, are necessary for muscle growth. Such ergogenic aids, that is supplements which stimulate muscle growth, include the three amino acids, leucine, isoleucine and valine (see paragraph [0004]). Furthermore, Phillips (1997) teaches that beta-hydroxy beta-methylbutyrate (HMB) is a metabolite of the essential amino acid leucine (see p. 66, "What is HMB?"). Phillips teaches that HMB up-regulate the ability to build muscle and burn fat, and may help decrease stress-induced muscle protein breakdown, and enhance increases in both muscle size and strength (see p. 66, "What do the scientific studies show?").

34. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings and optimize the amount of leucine in the composition to enhance the muscle performance. One of ordinary skill in the art would have been motivated to optimize the amount of leucine in the composition, since Allen teaches that leucine, isoleucine and valine are three amino acids that stimulate muscle growth, and Phillips teaches that leucine breaks down into HMB that build muscle, burn fat, and increases in both muscle size and strengths. One would be motivated to give leucine to produce the down stream compound HMB. Again, Leu, Ile and Val are well known to be used for stimulating muscle growth. Furthermore, in addition to "about" still allowing 23 to be 'about 30', the MPEP states that "Similarly, a prima facie case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties. *Titanium Metals Corp of America v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985)." See MPEP 2144.05. The artisan would have expected Leu to behave

the same at 25 or 30 or 35. Applicant's own example 4 shows clearly that Leu does not improve muscle building. The amount of protein synthesis and protein breakdown for both 25% leucine and 35% leucine was about the same for both leucine concentrations (see Table 4 of instant specification). Therefore, the differing concentrations of leucine would function the same. It appears that the additional components are important to the reduction of breakdown (see Table 4 of instant specification).

Furthermore, the MPEP further states: Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. *"[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)* (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 (*"The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969)* (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the

criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). Knowing that leucine, isoleucine and valine stimulate muscle growth, it would have been obvious to one or ordinary skill in the art to optimize the concentrations of leucine, isoleucine or valine to enhance the muscle growth. Furthermore, since leucine produces the down stream compound of HMB that is important in muscle growth and stimulation, it would have been obvious to optimize the concentration of leucine to produce the optimal composition. From the teachings of the references, it is apparent that one of the ordinary skills in the art would have had a reasonable expectation of success in producing the claimed invention.

Thus, the invention as a whole is *prima facie* obvious over the references, especially in the absence of evidence to the contrary.

Obviousness Double Patenting

35. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

36. Claims 1-4, 7-11, 13-14, 16, 23-27 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 5-11 of copending Application No. 12/110,016. Although the conflicting claims are not identical, they are not patentably distinct from each other because if one of ordinary skill in the art practiced the claimed invention of instant application, one would necessarily achieve the claimed invention of copending application, and vice versa.

37. Instant claims are drawn to a composition comprising: leucine and at least one essential amino acid selected from the group consisting of leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine, histidine, and combinations thereof in free and/or salt form.

38. Copending claims are drawn to a composition of matter comprising the essential amino acids L-histidine, L-isoleucine, L-leucine, L-lysine, L-methionine, L-phenylalanine, L-valine and L-threonine, wherein the concentration of L-leucine is not less than about 18% of the EAAs and not more than about 40% by weight of the EAAs composition.

39. Therefore, if one of ordinary skill in the art practiced the claimed invention of instant claims, one would necessarily achieve the claimed invention of copending application, and vice versa.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

40. Claims 1-4, 7-11, 13-14, 16, 23-27 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2, 5 and 7 of copending Application No. 12/366,520. Although the conflicting claims are not identical, they are not patentably distinct from each other because if one of ordinary skill in the art practiced the claimed invention of instant application, one would necessarily achieve the claimed invention of copending application, and vice versa.

41. Instant claims are drawn to a composition comprising: leucine and at least one essential amino acid selected from the group consisting of leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine, histidine, and combinations thereof in free and/or salt form.

42. Copending claims are drawn to a composition comprising a therapeutic component including: intact protein; and at least one essential amino acid selected from the group consisting of: leucine, isoleucine, valine, lysine, methionine, histidine, phenylalanine, threonine, and tryptophan; and a carrier component comprising a fruit juice.

43. Therefore, if one of ordinary skill in the art practiced the claimed invention of instant claims, one would necessarily achieve the claimed invention of copending application, and vice versa.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

44. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982. The examiner can normally be reached on Mon-Thurs, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Julie Ha/
Examiner, Art Unit 1654